ADDENDUM PREFACE

On November 1, 2004, the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) made available draft background review documents (BRDs) that provided information and data about the current validation status of four *in vitro* test methods for detecting ocular corrosives and severe irritants (Available: http://iccvam.niehs.nih.giv/methods/ocudocs/ocu_brd.htm). The four test methods were the Bovine Corneal Opacity and Permeability (BCOP) assay, the Hen's Egg Test - Chorioallantoic Membrane (HET-CAM) assay, the Isolated Chicken Eye (ICE) assay, and the Isolated Rabbit Eye (IRE) assay. These draft BRDs were based on published studies using the identified test methods, and other data and information submitted in response to a 2004 *Federal Register* (*FR*) request (Available: http://iccvam.niehs.nih.gov/methods/eyeirrit.htm)

The Interagency Coordinating committee on the Validation of Alternative Methods (ICCVAM) convened an Expert Panel meeting on January 11-12, 2005, to independently assess the validation status of these four *in vitro* test methods for identifying ocular corrosives or severe irritants (Available: http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). Public comments at the meeting revealed that additional relevant data was available that had not yet been provided in response to earlier requests for data. The Expert Panel recommended that the additional data be requested and that a reanalysis of the accuracy and reliability of each test method be conducted where appropriate.

In response to this recommendation, an *FR* notice was published on February 28, 2005 (Available: http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). The notice requested all available *in vitro* data on these four *in vitro* ocular irritancy test methods and corresponding *in vivo* rabbit eye test method data, as well as any human exposure data (either via ethical human studies or accidental exposure). A request for relevant data was re-sent directly to the primary developers or users of each test method. In response to these requests, additional *in vitro* test method data and corresponding *in vivo* rabbit eye test results were submitted for the BCOP, HET-CAM, and ICE test methods, which were used for the reanalyses in this BRD addendum.

Further clarification of hazard classification rules for severe irritants was also obtained subsequent to the release of the four draft BRDs. This change resulted in a small number of substances previously classified as nonsevere irritants now being classified as severe irritants (from 10 to 15, depending on the test method and the classification system used). However, this change necessitated a reanalysis of the accuracy and reliability of all four of the test methods, which are provided in this BRD addendum.

The original draft BRDs also provided an evaluation of the accuracy of each test method by chemical class. The chemical classes assigned to each test substance were revised based on a chemical classification system consistent with the U.S. National Library of Medicine's Medical Subject Headings (MeSH; Available: http://www.nlm.nih.gov/mesh), an internationally recognized standardized classification scheme. This scheme was used to

ensure consistency in classifying substances by chemical class among all the *in vitro* ocular test methods under consideration, and resulted in some chemicals being re-classified into different chemical classes. As a result, the accuracy of each test method by chemical class was reanalyzed; the results of each reanalysis are also provided in this BRD addendum.

The original BRD proposed a list of 89 reference substances that could be used for the optimization and/or validation of test methods proposed to identify severe and/or irreversible ocular effects. This reference substance list also was proposed as a source to use in selecting substances for performance standards and proficiency testing. The Expert Panel concluded that the list of proposed substances was fairly comprehensive in that the three major groups of products to which the eye is exposed (i.e., industrial chemicals, pharmaceuticals, cosmetics) were represented, and that individual substances were appropriately chosen. However, the Expert Panel also made several recommendations about the list of proposed reference substances. Additionally, the number of potential candidate substances was increased as a result of additional data provided in response to the February 2005 *FR* notice (Available: http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). Accordingly, a revised list of proposed reference substances has been developed and is provided in this BRD addendum.

This BRD addendum is available in electronic format on the ICCCVAM/NICEATM website (Available: http://iccvam.niehs.nih.gov/methods/ocudocs/reanalysis.htm); a paper copy can be obtained from NICEATM on request (niceatm@niehs.nih.gov). Comments from the public and scientific community are welcome and will be made available on the ICCVAM/NICEATM website (Available: http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). The information in the BRD addendum also will be provided to the Expert Panel for their review and comment.

The ICCVAM and its Ocular Toxicity Working Group (OTWG) will consider the Expert Panel report, the revised accuracy and reliability analyses, and any public comments in preparing its final test method recommendations. These recommendations will be made available to the public and provided to the U.S. Federal agencies for consideration, in accordance with the ICCVAM Authorization Act of 2000 (Public Law 106-545) (Available: http://iccvam.niehs.nih.gov/about/PL106545.pdf).

We want to again acknowledge the excellent cooperation and contributions from the many organizations and scientists who provided critical data and information necessary for the original BRD and this addendum. The efforts of the many individuals who contributed to the preparation of this addendum also are gratefully acknowledged. These include Drs. David Allen and Neepa Choksi, Mr. Bradley Blackard, and Mr. James Truax, of Integrated Laboratory Systems (ILS), Inc., the NICEATM Support Contractor, as well as the members of the ICCVAM OTWG and ICCVAM representatives who reviewed various drafts. We also acknowledge Dr. Raymond Tice for his efforts in developing and reviewing this addendum as the Principal Investigator of the ILS, Inc. NICEATM Support Contract until June 26, 2005, when he became the Deputy Director of NICEATM. Finally, we want to recognize the excellent leadership of the OTWG Co-chairs, Dr. Karen Hamernik (U.S. Environmental Protection Agency) and Dr. Jill Merrill (U.S. Food and Drug Administration).

William S. Stokes, D.V.M. Diplomate A.C.L.A.M.
Director, NICEATM
Executive Director, ICCVAM

Leonard Schechtman, Ph.D.
U.S. Food and Drug Administration
National Center for Toxicological Research
Chairman, ICCVAM

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